Review Article

SELECTIVE COX-2 INHIBITORS

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ABSTRACT

Selective COX-2 inhibitors are relatively newer additions to the list of Non Steroidal Anti-Inflammatory Drugs (NSAID's). There efficacy is comparable to Diclofenac and Naproxen, but gastrointestinal tolerability is better than non-selective NSAID's. It has been observed that selective COX-2 inhibitors delay healing in gastrointestinal ulcers in animal modals, raising cautions in there use in patients with existing gastric ulcers. COX-2 inhibitors have similar effects on kidneys as other NSAID's. They may increase systolic blood pressure in hypertensive patients.

KEY WORDS: Celecoxib. Rofecoxib.

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications worldwide and are often the first choice of treatment for acute myalgias, orthopedic injuries, postoperative pain, chronic rheumatoid arthritis and osteoarthritis.

NSAID's inhibit the production of primary prostanoids by blocking the access of archidonic acid to the active site of cyclooxygenases (COX-2).

Prostonoids produced by cox-1 play a physiological role i.e. protection of gastric mucosa, platelet aggregation, vascular homeostasis and maintenance of renal sodium-water balance. Prostanoids produced by cox-2 take part in inflammatory response. Thus, it is said that NSAID's that are selective COX-2 inhibitors should theoretically be capable of maintaining NSAID's therapeutic properties, with fewer adverse effects due to the maintenance of prostaglandins production at normal physiological levels.

A classification has been proposed for COX-2 inhibitors[1]:

1. COX-1 selective inhibitors: Low-dosage aspirin.
2. COX- non-selective inhibitors: The majority of classified NSAID's.
3. COX-2 preferential inhibitors: Meloxicam and Nimesulide. They have fewer gastric side effects than standard NSAID's, but are not risk-free at high doses.
4. COX-2 Selective inhibitors: Celecoxib and Rofecoxib.

Selective COX-2 inhibitors have been recently marketed in Pakistan. There has been some concern about there side effects on gastrointestinal system cardiovascular system and kidneys. Extensive research work is being done all over the world to study their effects. Recently published literature is reviewed to highlight the efficacy and safety of these drugs.

PHARMACOKINETICS AND PHARMACODYNAMICS

Celecosib: When given orally, peak plasma drug concentration occurs after two to four hours. It is extensively protein bound, primarily to plasma albumin. The area under the plasma concentration time curve (AUC) of celecoxib increases in proportion to increasing oral doses between 100 and 800 mg. Celecoxib is eliminated following biotransformation to carboxylic acid glucuronide metabolites that are excreted in urine and faeces, 2% eliminate unchanged in urine. Celecoxib is metabolized primarily by the cytochrome P450 (CYP) 2C9 isoenzyme and has an elimination half-life of about 11 hours in healthy individuals.[2]

Rofecobix: The mean bioavailability of Rofecoxib at therapeutically recommended doses is approximately 93%. The area under the plasma concentration-time curve (AUC) is roughly dose proportional across the clinical dose range. The plasma concentration-time profile exhibits multiple peaks. The median time to maximal concentration (T-max) is 2-3 hours, with multiple dosing, steady-state conditions are reached by day 4. The Rofecoxib is approximately 87% bound to human plasma protein. Metabolism of Rofecoxib is primarily mediated through reduction by cytosolic enzymes. It is eliminated predominantly by hepatic metabolism with less than 1% unchanged drug recovered in urine.

DRUG INTERACTIONS WITH COXIBS

Coxibs are hepatically metabolized; Rofecoxib primarily through reduction by cytosolic enzymes and celecoxib by the cytochrome P450 (CYP), enzyme system. As Rofecoxib is not metabolized by CYP, it has fewer confirmed or potential drug interactions than Celecoxib. However, potent inducer of CYP such as rifampcin may decrease Rofecoxib concentration because of induction of general hepatic metabolic activity.[3]

Celecoxib is metabolized by CYP2C9 and may be increased or decreased by CYP2C9 modifiers. Celecoxib does not interact with warfarin, ketoconozole or methotrexate. Drug interaction with fluconozole and lithium has been documented.

The selective COX-2 inhibitor Celecoxib has a sulfonamide structure and is contraindicated for patients with known sulfa allergy.[4]

Efficacy: American College of Rheumatology (ACR) and the European League of Associations of Rheumatology (EUCAR) in their published recommendations for the use of pharmacological therapy in the treatment of patients with lower limb osteoarthritis have suggested the use of specific COX-2 inhibitors in patients with severe pain and/or signs of inflammation. They have also observed that specific COX-2 inhibitors have comparable efficacy of traditional dual inhibitor NSAID's. [5]

McKenna et al[6] conducted a clinical trial in 600 patients with osteoarthritis (OA) of the knee to test the hypothesis that the specific COX-2 inhibitors Celecoxib has equivalent efficacy and superior tolerability/safety profile when compared to diclofenac. They concluded that Celecoxib 200 mg daily is as effective as diclofenac 150 mg daily for relieving signs and symptoms of OA of the knee including pain and has a rapid onset of action. However, Celecoxib appears to have a superior safety and tolerability profile.

In the treatment of rheumatoid arthritis Celecoxib has shown similar clinical efficacy as conventional NSAID's.

Zacher J and Schattenkirchner M.[7] conducted a post marketing surveillance study to assess the efficacy and tolerability of Rofecoxib in the treatment of OA. Patients were eligible for inclusion in this study if they were being treated for the first time or being switched from other medications. More than three-quarters of the 80,371 patients enrolled in the study reported improved pain relief and function during treatment with Rofecoxib (12.5 or 25 mg/day), including a reduction in pain experienced when walking on a flat surface or climbing or descending stairs. A majority of patients also considered that the duration of analgesia provided by Rofecoxib was longer than with previous medications (predominantly non-steroidal anti-inflammatory drugs).

EFFECTS ON GASTROINTENTINAL TRACT

Two double blinded randomized outcome trials were conducted to determine the incidence of clinical GI events with the Rofecoxib and Celecoxib compared with non-selective NSAID's. The VIGOR study (Vioxx gastrointestinal outcomes research) compared Rofecoxib with naproxen, and CLASS study (Celecoxib long-term arthritis safety study) compared Celecoxib with Ibuprofen and diclofenac.

The VIGOR trial revealed a relative risk reduction for clinical upper GI events of 50% with Rofecoxib, and a 60% reduction in complicated events. In the CLASS study the 23% reduction in complicated ulcers with Celecoxib did not reach statistical significance (P=0.45), although when all clinical events were examined, the 34% reduction was significant (P=0.04). However, low-dose aspirin use, which was allowed in the CLASS study, may have influenced the result. A subgroup analysis in the patient who did not take aspirin revealed a non significant 45% reduction in complicated events with Celecoxib (P=0.19) and a 47% reduction in complicated and symptomatic ulcers (P=0.02). [8]

Proton pump inhibitors are widely used by patients and physicians for the treatment of GI symptoms and duodenal ulcer. Wolfe F et al[9] reported increased risk of upper GI ulcers in concomitant use of proton pump inhibitors and NSAID's, regardless of which NSAID is used.

Laudanno OM et al[10] studied the effect of Celecoxib and Rofecoxib in experimental model developed in different groups of wistar rats. They reported that Celecoxib or Rofecoxib, either orally or subcutaneously did not produce necrotic lesions in healthy gastrointestinal mucosa. In contrast, previously indomethacin-induced lesions were aggravated. Models in which gastric and duodenal ulcers were induced by acetic acid and cystamine, develop total necrosis in the small intestine as well as increased ulcers and perforation of gastric and duodenal ulcer. The author concluded that dose dependent administration of Celecoxib and Rofecoxib as COX-2 inhibitors and non-cox-1 inhibitors respectively did not produce toxic injuries on healthy gastrointestinal mucosa, thus providing broad therapeutic spectrum. On the other hand, when administered in presence of altered gastrointestinal mucosa, they worsened and complicated gastric ulcers, and also induce necrosis in the small intestine, thereby restricting their clinical use.

In another similar study, Guo JS et al[11] reported that

gastric ulcers induce by application of acetic acid solution in male Sprague-dawley rats, significantly increased in size when Rofecoxib was administered at the dose of 10mg/kg/day for 14 days. It decreased the number of micro vessels, basic fibroblast growth factor and concentration of prostaglandin E (2) level in the ulcer base at day 6. The finding that highly selective COX-2 inhibitors delayed ulcer healing in rats and impaired angiogenesis in the ulcer base raise cautions regarding the use of COX-2 inhibitors in patients with gastric ulcers.

EFFECTS ON CARDIOIVASCULAR SYSTEM

Atherosclerosis is a process with inflammatory features and COX-2 inhibitors may potentially have anti atherogenic effects.

Ray W et al[12] conducted a retrospective cohort study of individuals on the expanded Tennessee Medicaid programme (TennCare), in which they assessed occurrence of serious coronary heart disease (CHD) in non-users (n=202916) and in users of Rofecoxib and other NSAID's (Rofecoxib n=24,132, other n=151,728). Participants were aged 50-84 years, lived in the community, and had no life-threatening non-cardiovascular illness. Users of high-dose Rofecoxib were 1.70 (95% CI 0.98-2.95, p=0.058) times more likely than non-users to have CHD; among new users this rate increased to 1.93 (1.09-3.42, p=0.024). By contrast, there was no evidence of raised risk of CHD among users of Rofecoxib at doses of 25 mg or less or among users of other NSAID's.

Concomitant use of NSAID's including the cyclooxygenase-2 (COX-2) specific inhibitors, with antihypertensive medication is common practice for many patients with arthritis.

Whelton A et al[13] conducted a study to evaluate the effects of Celecoxib 200 mg/day and Rofecoxib 25 mg/day on blood pressure (BP) and edema in a 6-week, randomized, parallel-group, double-blind study in patients $\geq$ 65 years of age with osteoarthritis who were treated with fixed antihypertensive regimens. One thousand ninety-two patients received study medication (Celecoxib, n = 549; Rofecoxib, n = 543). Significantly more patients in the Rofecoxib group compared with the celecoxib group developed increased systolic BP (change >20 mm Hg plus absolute value $\geq$140 mm Hg) at any time point (14.9% vs. 6.9%, p <0.01). Rofecoxib caused the greatest increase in systolic BP in patients receiving angiotensin-converting enzyme inhibitors or beta blockers, whereas those on calcium channel antagonists or diuretic monotherapy receiving either Celecoxib or Rofecoxib showed no significant increases in BP. Clinically significant new-onset or worsening edema associated with weight gain developed in a greater percentage of patients in the Rofecoxib group (7.7%) compared with the Celecoxib group (4.7%) (p <0.05). Thus, in patients with controlled hypertension on a fixed antihypertensive regimen, careful monitoring of BP is warranted after the initiation of Celecoxib or Rofecoxib therapy.

EFFECTS ON RENAL FUNCTION

Non steroidal anti-inflammatory drugs can affect renal function in a variety of ways. The most important clinical effects are decreased sodium excretion, decreased potassium excretion, and declines in renal perfusion. Decreased sodium excretion can result in weight gain, peripheral edema, attenuation of the effects of antihypertensive agents, and rarely precipitation of chronic heart failure. Hyperkalemia can occur to a degree sufficient to cause cardiac arrhythmias. Renal function can decline sufficiently enough to cause acute renal failure. Risk factors for all of these effects have been identified, allowing prospective identification of patients at risk with institution of appropriate precautionary measure. All NSAID's seem to share these adverse effects. Preliminary data from cyclooxygenase-2-selective inhibitors suggest that they also affect renal prostaglandins. Therefore, the same cautions should be exercised with their use as with traditional NSAIDs.[14]

A study conducted by Zhao SZ [15], sought to compare renal safety signals between the COX-2-specific inhibitors Rofecoxib and Celecoxib, based on spontaneous reports of adverse drug reactions (ADRs) in the World Health Organization/Uppsala Monitoring Centre (WHO/UMC) safety database through the end of the second quarter of 2000.

As with traditional NSAID's, both COX-2-specific inhibitors were associated with renal-related ADRs. However, the adverse renal impact of Rofecoxib was significantly greater than that of Celecoxib.

Celecoxib was shown to have a similar renal safety profile to that of diclofenac and ibuprofen. This analysis indicates that Rofecoxib has significantly greater renal toxicity than Celecoxib or traditional NSAID's. This negative renal impact may have the potential to increase the risk for serious cardiac and/or cerebrovascular events.

CONCLUSION

Coxibs are a major advance in the therapy of patients with painful and inflammatory conditions. There efficacy in relieving pain is similar to diclofenac and naproxen. These drugs have high gastrointestinal safety, although there use in patients with existing gastric ulcers is not advisable. In hypertensive patients, these drugs may raise the systolic blood

pressure. Constant check of blood pressure is recommended. Selective Cox-2 inhibitors should be used with caution in patients with renal impairment.

Celecoxib has a sulfonamide structure. Even though serious sulfonamide reactions are rare, their clinical impact on patient safety warrants close monitoring. Physicians should be aware of possible sulfonamide allergy when prescribing Celecoxib.

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